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Impaired sleep-related consolidation of declarative memories in idiopathic focal epilepsies of childhood

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ABSTRACT

Objective: Declarative memory is consolidated during sleep in healthy children. We tested the hypothesis that consolidation processes are impaired in idiopathic focal epilepsies (IFE) of childhood in association with frequent interictal epileptiform discharges (IEDs) during sleep.
Methods: A verbal (word-pair association) and a nonverbal (2D object location) declarative memory task were administrated to 15 children with IFEs and 8 control children 6–12 years of age. Patients had either centrotemporal (11 patients) or occipital (4 patients) IEDs. All but 3 patients had a history of unprovoked seizures, and 6 of them were treated with valproate (VPA). The learning procedure (location of object pairs presented on a grid; association of word pairs) was executed in the evening. Retrieval was tested immediately after learning and on the next morning after a night of sleep. Participants were tested twice, once in natural home conditions and one month later in the unfamiliar conditions of the sleep unit under EEG monitoring.
Results: Overnight recall performance was lower in children with IFE than in control children on both tasks ($ps < 0.05$). Performance in home conditions was similar to that in hospital conditions. Higher spike–wave index (SWI) during nonrapid eye movement (NREM) sleep was associated with poorer performance in the nonverbal task ($p < 0.05$). Valproate treatment was not associated with overnight recall performance for both tasks ($ps > 0.05$).
Conclusion: Memory consolidation is impaired in IFE of childhood. The association between higher SWI during NREM sleep and poorer nonverbal declarative memory consolidation supports the hypothesis that interictal epileptic activity could disrupt sleep memory consolidation.

1. Introduction

Idiopathic focal epilepsies (IFE) of childhood are age-related epileptic conditions of presumed genetic origin, generally characterized by infrequent and brief focal seizures easily controlled with medication and interictal epileptiform discharges (IEDs) during wakefulness becoming more abundant during sleep [1]. They have a good prognosis without major cognitive deficits and seizure remission expected before the end of adolescence [2]. The two most common epileptic syndromes are benign epilepsy with centrotemporal spikes (BECTS) and benign childhood epilepsy with occipital paroxysms (BCEOP) defined according to clinical and electroencephalographic (EEG) features [2]. In the past 15 years, numerous studies have reported an unexpected high rate of cognitive difficulties in the language, attention, and memory domains, challenging the "benign" label of these epilepsies [3–5]. The pathophysiology of these cognitive deficits still remains controversial as various factors are likely to impact cognitive abilities in children with epilepsy, including the underlying etiology, the use of antiepileptic drugs (AEDs), the occurrence of seizures, and the presence of interictal epileptiform discharges (IEDs) [6–8]. The hypothesis that IEDs exert an influence on cognitive processes in IFE is supported by associations between behavioral/cognitive difficulties and IED severity at the acute phase of the disease. In addition, the normalization of the EEG signal usually reverts these cognitive alterations [2–4]. However, the underlying pathophysiological mechanisms remain largely speculative (see [8] for a review).

Studies performed in healthy children have shown that nonrapid eye movement (NREM) sleep participates in the consolidation of both verbal and nonverbal declarative memories, indicating improved performances after sleep compared with wakefulness (see [9,10] for review). As IEDs are particularly abundant during NREM sleep in IFE, it has been proposed that IEDs may interfere with the physiological

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neuroplasticity processes subtending learning and memory consolidation during sleep [8,9,11,12]. Supporting this hypothesis, a pilot study disclosed impaired sleep-related consolidation of verbal declarative memories in 4 patients with various forms of IFEs compared with healthy children [13]. Furthermore, IFE were associated with continuous spikes and waves during slow-wave sleep (CSWS) in two patients. In one case, administration of corticosteroids completely normalized both the sleep EEG and the memory consolidation [13]. Another pilot study performed in 10 children with epilepsy with similar amount of IEDs during wakefulness and sleep showed no advantage of sleep for memory consolidation [14]. These preliminary results indicate that IEDs in IFE might, indeed, disrupt the brain plasticity processes underlying sleep-related memory consolidation.

In the current study, we investigated the impact of IEDs and AED intake on memory consolidation during sleep using a verbal and a nonverbal declarative memory task in a population of children with IFEs and matched controls. The use of a nonverbal memory task allowed the investigation of the impact of IEDs in younger children who are not yet proficient with literacy. Additionally, we tested the extent to which a night of sleep in an unfamiliar hospital setting may dampen sleep-related memory consolidation performance compared with a night of sleep spent at home in the children's natural environment.

2. Methods

2.1. Patients and subjects

Fifteen patients with IFE 6–12 years of age (9 boys; mean ± standard deviation (SD): 9 ± 1.7 years) and eight healthy control children 7–12 years of age (3 boys; mean ± SD: 9.5 ± 1.5 years) consented to participate in this study approved by the Biomedical Ethics Committee of the ULB-Erasme Hospital. Parents gave written informed consent. Control children were recruited from public schools. They had no known learning, language, or neurological problems and reported a regular sleep–wake rhythm and no sleep disorder.

Patients with IFE fulfilled the following inclusion criteria: (1) a standard wake EEG evocative of BECTS or BCEOP, i.e., a normal background and at least one focus of spikes–waves either in the centrotemporal region (maximum electronegativity at electrodes C3, C4, T3, or T4 according to the international 10–20 electrode placement system) or in the occipital region (maximum electronegativity at electrodes O1 or O2); (2) a normal neurological examination; (3) an absence of mental retardation (performance IQ > 80); and (4) an absence of significant behavioral difficulties. None of the parents reported a regression in the behavior and/or performances of their children at the time of the inclusion in the study.

Demographic data for patients are summarized in Table 1. Epilepsy was diagnosed in 12 patients who presented at least one unprovoked epileptic seizure with semiology typical for either BECTS (n = 9) or BCEOP (n = 3). The 3 other patients had IEDs located either in the centrotemporal regions (n = 2) or in the occipital regions (n = 1), fortuitously discovered in the context of the evaluation of an attention deficit disorder without a history of seizures. Structural magnetic resonance imaging (MRI) was obtained in all but one patient, and no brain abnormality was detected. Nine children were drug-free at the time of the assessment, and 6 were taking valproate (VPA). Epilepsy was well controlled in all patients at the time of investigation, and no clinical seizures occurred during the entire experiment. Declarative learning abilities were assessed in children with IFE and control children using the List Memory subtest (learning of a word list of 15 words) of the NEPSY — French version [15] and are detailed in Table 1 for the patients. Verbal abilities were evaluated with a naming task (E.L.O.; [16]), a verbal comprehension task (E.C.O.S.S.E.; [17]), a vocabulary task (EVIP; [18]), and a test of pseudoword repetition (NEPSY; [15]). For these 4 tests, the scores of all children were between −1.5 and +1.5 standard deviation from the mean.

2.2. Experimental paradigms

Nonverbal declarative memory was tested using a two-dimensional (2D) object location task adapted from Rasch et al. [19]. Verbal declarative memory was tested using a word-pair learning task used in our previous pilot study [13].

2.2.1. 2D object location memory task (Fig. 1, left panel)

The 2D object location memory task consisted of 12 pairs of cards depicting, in color, animals and everyday objects. Two parallel versions of the task were created using different pictures and different locations. The order of the versions was counterbalanced across subjects and sessions. Pictures were selected out of fifty 2D drawings created for another study [20]. All 24 possible spatial locations on a grid were shown as gray squares on a 15-inch flat screen (see Fig. 1 for details). During the learning session, children were asked to memorize the locations of each pair of identical cards. During the immediate recall, one card was first presented, and the children were asked to locate the position of the associated card on the grid (cued recall procedure). Children received a feedback on their accuracy, and the immediate recall of the 12 card pairs (correct and incorrect locations) was repeated until they reached the criterion of 60% correct responses. The next morning, they were asked again to recall the location of each twin card (delayed retrieval). The procedure was identical to the immediate recall phase except that no feedback was given and no criterion had to be reached.

Table 1
Patients' demographic data.

Patient number	Gender	Age	Age at epilepsy onset	Localization of IEDs	AED	Epileptic syndrome	Memory task	PRI	Words list
1	M	11	9	C3, C4	VPA	BECTS	V	84	14
2	F	8	1	C3	VPA	BECTS	NV	100	12
3	F	7	4	O1, O2	VPA	BCEOP	NV	88	10
4	F	7	2	C4	VPA	BECTS	NV	87	10
5	M	6	5	C3	None	BECTS	NV	86	11
6	M	9	8	C3	VPA	BECTS	V	90	8
7	M	9	7	C3, C4	VPA	BECTS	V	81	7
8	F	7	6	O1, O2	None	BCEOP	NV	80	7
9	M	8	5	O2	None	BCEOP	V	87	11
10	M	7	6	C4, O1	None	BECTS	V	109	9
11	M	11	/	T3	None	NE	V, NV	85	10
12	F	12	11	T4	None	BECTS	V, NV	88	14
13	M	7	/	O2	None	NE	V, NV	92	10
14	F	9	7	T3, C4	None	BECTS	V	90	12
15	M	10	/	C4	None	NE	V, NV	92	14

M = male; F = female; IEDs = interictal epileptiform discharges; AED = antiepileptic drug; VPA = valproate; BECTS = benign epilepsy with centrotemporal spikes; BCEOP = benign childhood epilepsy with occipital paroxysms; NE = not epileptic; V = verbal memory task; NV = nonverbal memory task; PRI = Perceptual Reasoning Index of the WISC-IV (mean = 100, SD = 15); word list = list of memory of the NEPSY [15] (mean = 10, SD = 3).

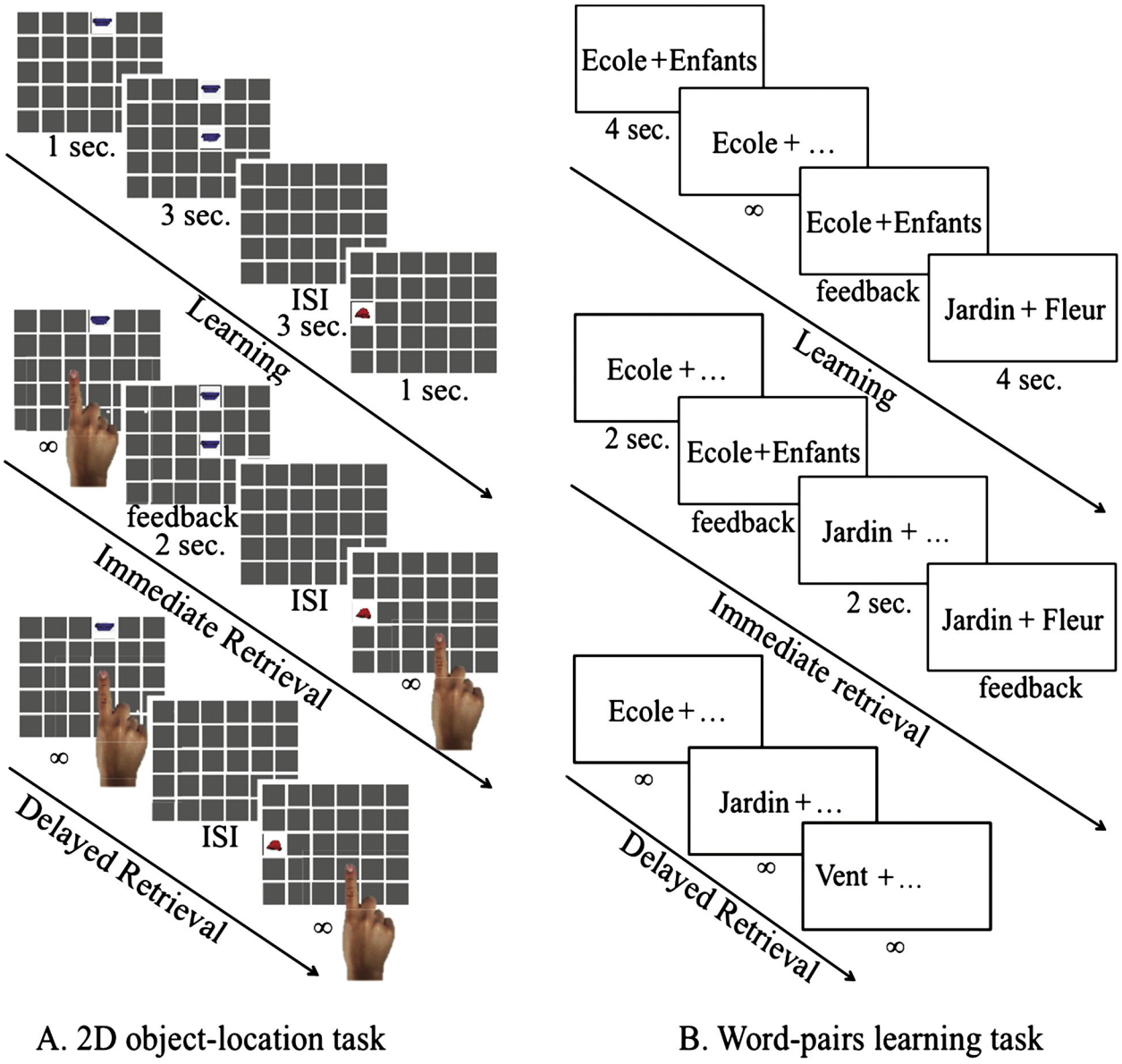

Fig. 1. Memory tasks. (A) 2D object location memory task. At learning, all the card locations are presented twice in a random order. The first card is always presented first followed by both card locations. At immediate retrieval, children have to indicate the locations of the 2D card with a cued recall procedure and visual feedback after the response. The delayed retrieval follows the same procedure except that no feedback is provided. (B) Word-pair learning task. At learning, each presentation of a word pair is followed by an immediate recall. Correct feedback is provided after an incorrect answer. At immediate retrieval, children have to recall the 2nd word of the pair with a cued recall procedure. Feedback is provided after an incorrect response. The delayed retrieval follows the same procedure except that no feedback is provided. ISI = interstimulus interval. ∞ = until a response is provided.

2.2.2. Word-pair learning task (Fig. 1, right panel)

The word-pair learning task was exactly the same as the one described in Urbain et al. [13]. During the learning session, children were asked to memorize all the semantically related word pairs (32 for children 9–11 years of age or 22 for children 7 and 8 years of age). They were first presented with a pair of words followed by the first word of that pair (cued recall procedure). They were asked to recall the second word of the pair, and feedback was given in the case of incorrect answer. After all the word pairs were presented, children responded to an immediate retrieval test with the same cued recall procedure as during learning until the criterion of 60% of the word pairs learned was reached. During the delayed retrieval, subjects were asked again to recall the word pairs, but no feedback was given, and no criterion had to be reached.

2.3. Experimental procedure

Controls and participants with IFE were administered twice the verbal and nonverbal tasks, once at home (familiar environment) and once at the hospital (unfamiliar environment) where they underwent polysomnographic recordings during the posttraining night. During a first session at home, children were administered the learning tasks in the evening, slept normally, and were retested on the following morning. About 1 month later, a second session occurred at the sleep unit in the hospital environment, and children were administered other versions of the same learning tasks in the evening, slept under continuous video-EEG control, and were then retested on the following morning. Although control children were administered both tasks in both experimental environments, the nonverbal memory task was not administered to patients investigated before August 2012 since the first protocol only included the verbal memory task (patient numbers 1, 6, 7, 9, 10, and 14). Comparisons were, thus, conducted between 9 patients with IFE and 8 age-matched control children for the nonverbal task and between 10 patients with IFE and 8 age-matched control children for the verbal task (see Table 1). The children (patients and controls) who performed both tasks were evaluated during the same session, the 2D object location memory task being presented first followed after a

short break by the word-pair learning task. For each session, learning and immediate retrieval occurred around 8 pm in the evening. Delayed retrieval after a night of sleep took place on an average of 60 min after awakening to minimize potential effects of sleep inertia on performance [21]. The time interval between learning and retrieval was about 11 h.

Before each retrieval session (immediate and delayed), the Psychomotor Vigilance Task (PVT) [22] was administered to control for possible effects of circadian variations (i.e., morning versus evening) of vigilance on learning and memory performances [23]. The PVT features a simple reaction time task in which subjects must press a button as fast as possible each time a digital counter starts. The interstimulus interval is randomly set from 2 to 10 s. The task duration was 5 min, and the dependent measure was reaction times.

2.4. Polysomnographic and EEG recordings

Sleep was recorded with the Brainlab system (OSG, Belgium) using 12 to 21 EEG electrodes positioned according to the 10–20 International System plus additional bipolar electrodes to record eye movements, electrocardiogram, and surface electromyogram of the chin. Sleep recordings were visually scored by two experts (RL and GD) according to standard criteria [24] using the PRANA software (PhiTools™, Strasbourg, France). In patients, the frequency of IEDs during NREM sleep was computed by calculating a spike–wave index (SWI) using a previously published automatic spike detection algorithm [25] applied on the entire NREM sleep time. The algorithm failed to detect IEDs in 4 patients who showed either low-amplitude IEDs or IEDs located close to the midline. For these children (patient numbers 2, 5, 12, and 15), SWI calculation was performed manually as previously described [26] on the first 30-minute EEG recording of NREM sleep. Then, we tested the hypothesis of a difference between SWI calculated on the first 30-minute EEG recording of NREM sleep and SWI calculated on the entire NREM sleep time in the 11 patients with automatically determined SWI. This hypothesis was not verified (38 ± 6.4 versus 41 ± 6.8; $p > 0.1$). We, thus, concluded that IED quantification on the first 30 min of NREM sleep was reliable to assess the rate of interictal spiking during NREM sleep. Table 2 provides results of SWI determined on the first 30-minute EEG recording of NREM sleep for all patients. These data are used for further statistical analyses. Interictal epileptiform discharges were also qualitatively characterized according to their diffusion over the scalp using an adapted version of the grading system previously reported [26]: grade 0 = normal; grade 1 = unique focus of spikes with regional diffusion; grade 2 = multiple foci of spikes with regional diffusion; grade 3 = at least one focus of spikes and waves diffusing either over the entire homolateral hemisphere or to the contralateral homologue region; and grade 4 = at least one focus of spikes and waves diffusing over the whole scalp. Additionally, the wake EEG records of the patients were inspected. In all patients, the rate of IEDs was lower at awake than during NREM sleep, but movement artifacts precluded precise quantification of IEDs. In 2 patients (numbers 12 and 15), no IEDs could be detected on wake EEG. In the other patients, the diffusion of the IEDs over the scalp, as assessed by the grade system, was similar at awake than during NREM sleep, and the topography of the foci was also similar.

2.5. Statistical analyses

Data are expressed as mean ± standard deviation. Statistical analyses were performed using Statistica 7.0 (StatSoft Inc., Tulsa, OK). Comparisons between patients with IFE and healthy control children and between children under AED and drug-free children with IFE were conducted using independent t-tests. Pearson chi-square tests compared the distribution of boys with that of girls between groups.

Memory consolidation between patients and controls was tested using repeated measures ANOVA on the percentage of correct responses with Environment (home versus hospital) and Retrieval (immediate versus delayed) as within-subject factors and Group (patients versus control children) as a between-subjects factor. Newman–Keuls post hoc tests were used when appropriate in ANOVA analyses.

Additionally, linear regression analyses were computed using a memory consolidation score (i.e., % of items recalled at delayed retrieval minus % of items recalled at immediate retrieval) as a dependent factor and independent IFE-related predictors.

Finally, repeated measures ANOVA was computed on mean reaction times (RTs) of the PVT with the within-subject factors Environment (home versus hospital) and Retrieval (immediate versus delayed) and with the between-subjects factor Group.

Table 2
Individual sleep variables for each patient. Mean ± SD is reported for both patients and control children.

Patient number	SPT (min)	WASO (%)	REM (%)	NREM (%)	Stage 1 (%)	Stage 2 (%)	SWS (%)	EEG grades	SWI sleep
1	564	2	18	80	1	29	50	3	29%
2	589	3	17	80	6	49	25	1	29%
3	625	6	15	79	2	36	41	3	66%
4	580	4	20	76	6	40	30	0	0%
5	540	4	14	82	2	55	25	1	10%
6	509	19	14	67	2	29	36	3	52%
7	485	3	26	71	5	52	14	2	36%
8	645	2	8	90	2	35	53	4	65%
9	477	13	11	76	3	35	38	1	32%
10	564	7	16	77	1	37	39	2	40%
11	467	14	14	72	4	44	24	3	42%
12	549	16	9	75	3	47	25	1	10%
13	611	5	15	80	2	46	32	3	32%
14	578	18	16	66	1	41	24	2	63%
15	530	4	16	80	3	42	35	1	8%
Means[a]	571 ± 55	6 ± 5	14 ± 3	79 ± 5	3 ± 2	44 ± 6	32 ± 10	2 ± 1	34 ± 17
Means[b]	536 ± 50	10 ± 6	15 ± 5	74 ± 5	2 ± 1	41 ± 7	30 ± 8	2 ± 1	29 ± 25
Controls	574 ± 78	8 ± 5	16 ± 4	79 ± 4	3 ± 1	38 ± 12	38 ± 11	0	0

SPT = sleep period time in minutes; WASO (%) = wake after sleep onset; REM (%) = rapid eye movement; SWS = slow-wave sleep; EEG grades = qualitative characterization of the EEG with the adaptation of a grading system [21]; SWI sleep = spike–wave index during NREM sleep.

[a] Means ± standard deviations (SDs) of patients with IFE who underwent the 2D object location memory task.

[b] Means ± SDs of patients with IFE who underwent the word-pair learning task.

3. Results

3.1. Demographic data, learning abilities, and vigilance

Comparisons between subsets of patients with IFE and control children failed to disclose age or sex differences (ps > 0.45). Declarative learning ability as measured using the NEPSY List Memory subtest did not significantly differ between these subsets of patients with IFE (patients who performed the nonverbal memory task: recall of 10.8 ± 2.2 words; patients who performed the verbal memory task condition: recall of 11.1 ± 1.7 words) and control children (recall of 10.8 ± 2 words; ps > 0.06).

Vigilance as assessed using the PVT was also similar between patients with IFE and control children. Indeed, analyses of variance conducted on mean RTs failed to disclose any significant effect of Retrieval (immediate versus delayed), Environment (home versus hospital), Group (patients versus controls), or interaction (all ps > 0.08).

3.2. Polysomnographic data

Data are summarized in Table 2. Comparisons between subsets of patients with IFE and control children failed to disclose differences in sleep measures (ps > 0.09 for all comparisons). Sleep measures were also similar between patients taking VPA and AED-free patients (ps > 0.37), but a higher percentage of time spent in stage 1 sleep in medicated children with IFE ($t(13) = 2$; $p = 0.005$) was found. Of note, patient 4, a girl with typical BECTS, had a normal EEG (grade 0) during the polysomnographic recording, but the standard wake EEG showed abundant centrotemporal IEDs at inclusion 10 months earlier. This case illustrates intrapatient variability of IEDs and emphasizes the need to record the EEG during the postlearning sleep.

3.3. Sleep-related memory consolidation

Memory performances for both the object location and word-pair tasks at immediate and delayed retrievals for control children and patients with IFE are shown in Fig. 2.

3.3.1. Nonverbal declarative memory (2D object location task)

The number of presentations of the cards to reach the 60% criterion at learning during both sessions was similar between the 2 groups (ps > 0.33). The analysis of variance disclosed a significant main effect of the Group ($F(1,14) = 9.4$; $p = 0.009$), with control children showing better memory performance compared with patients (71 ± 3% versus 60 ± 3%). The interaction Group × Retrieval was also significant ($F(1,15) = 13$; $p = 0.003$). Post hoc analyses revealed that while control children had similar percentages of correct responses at immediate and delayed retrievals (immediate: 69 ± 2% versus delayed: 73 ± 4%; p > 0.2), memory performance in patients significantly decreased after a night of sleep (immediate: 65 ± 2% versus delayed: 53 ± 4%; $p = 0.005$). The main effects of Environment and Retrieval failed to reach significance (ps > 0.08) as well as the interactions Environment × Group and Environment × Retrieval and the triple interaction Group × Environment × Retrieval (ps > 0.59).

3.3.2. Verbal declarative memory (word-pair learning task)

The number of presentations of the cards to reach the 60% criterion at learning during both sessions was similar between the 2 groups (ps > 0.48). Comparable with the nonverbal memory task, the analysis revealed a significant main effect of the Group ($F(1,14) = 4$; $p = 0.052$), with control children showing better learning performance compared with patients (84 ± 3% versus 76 ± 3%). The interaction Group × Retrieval was also found to be significant ($F(1,14) = 9$; $p = 0.027$). Post hoc analyses revealed that while control children improved their memory performance between immediate and delayed retrievals (81 ± 2% versus 87 ± 3%; $p = 0.008$), delayed recall of patients decreased after a night of sleep (81 ± 2% versus 71 ± 3%; $p < 0.003$). The interaction Environment × Group was also found to be significant ($F(1,14) = 6$; $p = 0.04$), but post hoc analyses only showed marginal differences in memory performance as control children were slightly better at the hospital than at home ($p = 0.09$). The main effects of Environment and Retrieval failed to reach significance (ps > 0.56) as well as the interactions Environment × Retrieval and Group × Environment × Retrieval (ps > 0.31).

3.3.3. Factors associated with memory changes in patients with IFE

We identified six factors that could influence memory consolidation in patients with IFEs: SWI during NREM sleep, EEG grades, the use of AEDs, a history of epileptic seizures, and the lateralization (left or right) and the localization of IEDs (centrotemporal or occipital). Since Spearman correlation analyses disclosed a positive correlation between SWI and EEG grade ($p = 0.005$; $r = 0.71$), the EEG grade was discarded from the analysis. The number of patients allowed the inclusion of two independent factors in our regression model. According to the available literature on factors that may impact cognition in children with epilepsy [6–8], SWI and the use of AEDs are the most likely contributing factors and were studied as potential predictors.

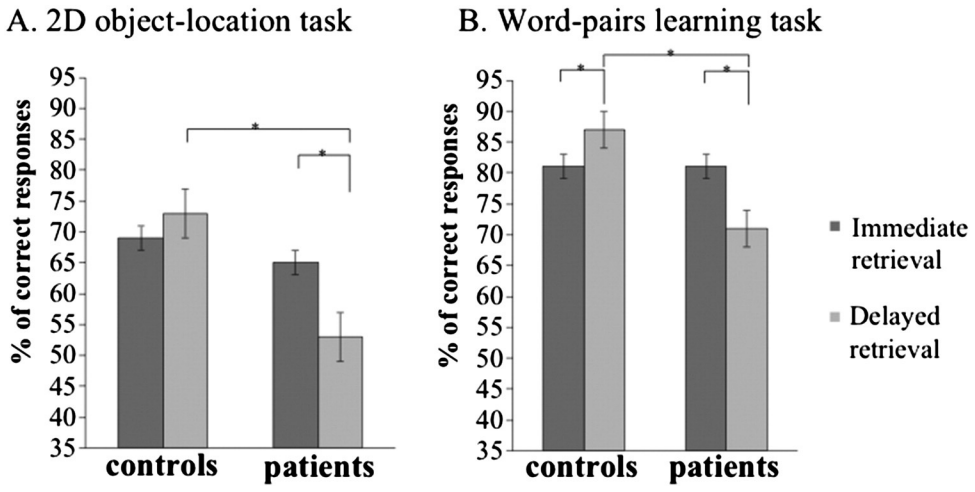

Fig. 2. Verbal memory consolidation and nonverbal memory consolidation in children with IFE and control children. Mean (±SD) % of correct responses at immediate (dark gray) and delayed (light gray) retrievals for (A) the card locations (2D object location memory task), and (B) the word pairs (word-pair learning task) in patients and controls. * = p < 0.05.

In the 2D object location memory task, the regression (R2) was statistically significant ($F(1,5) = 4.35$; $p = 0.038$; $r = 0.82$), with a significant effect of SWI ($t(2,5) = -2.08$; $p = 0.024$; $\beta = -0.61$) but not AEDs ($t(2,5) = -0.57$; $p > 0.53$; $\beta = -0.17$). Correlation analyses indicated that patients with the highest SWI were also those with the poorer memory score, i.e., a decrease in performance from immediate to delayed recall (Fig. 3).

In the word-pair learning task, the regression (R2) failed to reach statistical significance ($F(1,8) = 0.3$; $p > 0.28$; $r = 0.28$), indicating that neither the SWI nor the use of AEDs (Fig. 3) was associated with changes in memory performance.

4. Discussion

The present study showed that sleep-related consolidation of verbal and nonverbal declarative memories was significantly impaired in children with IFEs compared with control children, despite a learning performance within the normal range. Still, we confirmed results found by two studies, one of our research group in IFEs [13] and one of Sud et al. patients with drug-resistant epilepsy on polytherapy with focal symptomatic epilepsy mainly of temporal origin [14], showing poor memory consolidation during sleep in children with epilepsy.

To the best of our knowledge, our study is the first to investigate the impact of IEDs during sleep, as determined using a SWI, on the consolidation of two declarative memory tasks, one verbal task and one nonverbal task. We found a significantly positive association between the SWI and the extent of the deficit in memory consolidation in the nonverbal declarative memory task, supporting the hypothesis that IEDs during sleep could contribute to the deficits in memory consolidation in children with IFEs. However, this finding must be interpreted with caution because our study suffers from limitations. First, the number of patients was limited as only 9 out of the 15 patients were studied using the nonverbal task. Second, the SWI values were not ideally distributed among this subpopulation of 9 patients as 4 of them had relatively low SWI during sleep, which could affect the regression analysis. Third, our sample of patients was not homogenous in terms of ages, medication intake, and location of epileptic foci.

Analyses conducted in our population sample also revealed that deterioration of memory consolidation in children with IFE after a night of sleep was not related to the use of AEDs. This result is important because 6 of the 15 patients included in the study were taking AEDs. Moreover, patients treated with VPA exhibited an increased proportion of NREM stage 1 compared with control patients without treatment, confirming previous studies [27].

We found also that performance on both tasks was highly reproducible in two different sleep conditions, i.e., in a natural home condition and in the unfamiliar condition of the hospital sleep unit under polysomnography. This is an important practical finding since we are the first to show that investigation of sleep-related memory consolidation is not affected by the sleep conditions.

The neurophysiological processes subtending the consolidation of declarative memories during sleep remain speculative. Nowadays, two nonexclusive theories account for memory consolidation during sleep, i.e., the hippocampal–neocortical dialogue theory and the synaptic homeostasis hypothesis (for a review, see [9]). The hippocampal–neocortical dialogue theory proposes that declarative memory traces, initially encoded in the hippocampus, will be progressively transferred toward neocortical areas (particularly the medial prefrontal cortex and, if semantization occurs, the anterior temporal cortex) for long-term storage [28]. The neocortical slow oscillations of slow-wave sleep are thought to play a pivotal role in these processes by organizing the synchronization of thalamic spindles and hippocampal ripples that subtend the hippocampo-neocortical transfer of information during sleep [28,29]. At variance, the synaptic homeostasis theory proposes that synaptic strength is potentiated in memory-related neuronal networks during learning in the awake state, leading to saturation in the synaptic space and decreased use-dependent plasticity. During NREM sleep, a local use-dependent, homeostatic increase in slow oscillations contributes to bring back synaptic space to baseline and restore plasticity in the network while at the same time leaving an imprint of the memory in the cortex. In line with this theory, task-specific increase of slow activity in learning-related areas during NREM sleep was found to be positively correlated with overnight gains in performance [30]. Studies performed in atypical cases of IFEs, complicated by the occurrence of CSWS, suggest that abundant epileptic activity during sleep could impair these processes at different levels. Classical IFEs and IFEs complicated by CSWS are now recognized as a spectrum where the most frequent and diffuse IEDs during sleep result in more severe behavioral and cognitive deficits [31–33]. Therefore, one can assume that findings in atypical cases might be extended to classical IFEs. The impact of IEDs on synaptic downscaling processes was investigated in children with CSWS compared with healthy participants [34]. Results showed a progressive decrease in the slope of slow waves during a night of sleep in healthy children but not in CSWS children, suggesting an epilepsy-related disruption of synaptic homeostasis processes. Positron emission tomography studies in children with atypical rolandic epilepsy and CSWS have demonstrated profound cortical metabolic disturbances, distributed not only in areas involved by the IEDs but also in distant regions. These disturbances were sustained through the sleep–wake cycle but faded after the disappearance of CSWS [35,36]. Using EEG combined with functional magnetic resonance imaging (EEG–fMRI), Moeller et al. [32] showed evidence that patients with atypical rolandic epilepsy IED-associated

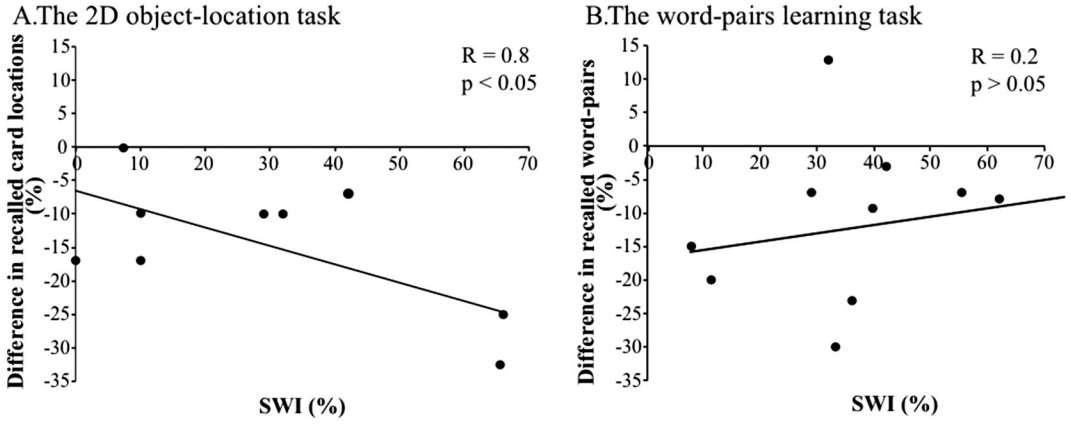

Fig. 3. Relationship between the changes in object location and word-pair retrievals from evening to morning (memory score) and the spike–wave index (SWI) during NREM sleep in patients with IFEs. (A) 2D object location memory task. Higher SWI is associated with lower memory performance. (B) Word-pair learning task. No significant correlation is disclosed (B).

had hemodynamic changes suggesting both activation and deactivation in various cortical and subcortical structures, including the frontal mesial cortex and the thalamus [32]. Finally, hippocampal dysfunction cannot be ruled out to explain poor sleep-related declarative memory consolidation in patients with IFE. Indeed, a study using proton magnetic resonance spectroscopy suggested abnormal hippocampal neuronal function that was correlated with IEDs in a group of children with BECTSs [37].

The number of patients in our sample prevented regression analyses on other factors that may impact memory performance in patients with IFE. Analyses failed to disclose an association between memory consolidation and the use of AEDs or the abundance of IEDs during sleep in the verbal memory task (word pairs). Other contributing factors could be the localization or the diffusion of IEDs. Wolff et al. [38] provided data supporting the hypothesis that centrotemporal and occipital IEDs might differently impact memory consolidation, disclosing a correlation between spike location and selective cognitive deficits in children with IFEs. In their study, children with occipital IEDs obtained lower performances in simultaneous information processing (especially in visual transformation tasks) compared with children with centrotemporal spikes, and children with left centrotemporal spikes performed worse in language tasks. In addition, dichotic listening studies suggested that deficits in BECTSs are contingent upon the lateralization of the epileptic discharges [39]. Finally, independent of the abundance of IEDs, it has been suggested that the diffusion of focal IEDs over the whole scalp may affect brain functioning; the more the discharges are diffused, the greater the impact will be [26,35]. In the present study, however, the positive correlation between EEG grades and SWI precluded the integration of the EEG grade as an independent factor in regression analyses.

Another factor that might explain poor memory consolidation in IFEs is the occurrence of seizures, which appeared in the past history of most patients but not in all of them. One may hypothesize that epileptic seizures will differently impact memory consolidation processes than just will epileptiform abnormalities (i.e., IEDs). Since none of the children with epilepsy included in this study had seizures during the days that preceded the experiment, this hypothesis is unlikely. The underlying genetic mutation may also explain poor memory consolidation in our patients. Idiopathic focal epilepsies are presumed to be genetically determined [1], but the only identified gene up to now is GRIN2A, a mutated gene in some patients with atypical BECTSs and Landau–Kleffner syndrome [40–42]. In the present study, patients were not genotyped. Therefore, we cannot exclude that the type of underlying genetic mutation impacts sleep-related memory consolidation processes, a hypothesis that should be tested in further studies. However, genotype is clearly not the only determinant of cognitive impairment in IFEs, as illustrated in families of patients with classical BECTSs, in whom relatives with epilepsy may have a much more severe phenotype with CSWS and major cognitive impairments [43].

In summary, our study brings new evidence supporting the hypothesis that IFE should not be considered as a paroxysmal dysfunction limited to the region of the cortex that generates IEDs. It should rather be envisioned as a dysfunction of a complex neural system sustaining various physiological functions, including sleep-related memory consolidation processes, in line with the definition of a "system epilepsy" proposed by Avanzini et al. [44].

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Ethics

The work described here is consistent with the Journal's guidelines for ethical publication.

Disclosure of conflicts of interest

None of the authors has any conflict of interest to disclose.

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